Abstract

Gene expression profiling of tumors, clinically designated as either metastatic (M+) or non-metastatic (M0), identifies genes whose expression differed significantly between classes. A class-prediction algorithm based on these medulloblastoma genes assigned the sample class to these tumors (M+ or M0) with 72% accuracy and to four additional independent tumors with a 100% accuracy. Class prediction also assigned the metastatic medulloblastoma cell line Daoy to the metastatic class. Notably upregulated in the M+ tumors were platelet derived growth factor receptor alpha (*PDGFRA*) and members of the downstream RAS/mitogen-activated protein kinase (*MAPK*) signal transduction pathway. Immunohistochemical validation on an independent set of tumors showed significant overexpression of *PDGFRA* in M+ tumors as compared to M0 tumors. In *in vitro* assays, PDGFA enhanced medulloblastoma migration and increased downstream *MAP2K1 (MEK1), MAP2K2 (MEK2), MAPK1 (p42 MAPK), and MAPK3 (p44 MAPK)* phosphorylation in a dose-dependent manner. Neutralizing antibodies to *PDGFRA* or U0126, a highly specific chemical inhibitor of *MAP2K1* and *MAP2K2* known as U0126, blocked *MAP2K1*, *MAP2K2*, and *MAPK1/3* phosphorylation, inhibited migration, and prevented *PDGFA*-stimulated migration. These results provide the first insight into the genetic regulation of medulloblastoma metastasis and are the first to suggest a role for and the *RAS/MAPK* signaling pathway in medulloblastoma metastasis. Inhibitors of *PDGFRA* and *RAS* proteins, among others overexpressed M+ genes identified herein, represent novel therapeutic targets in medulloblastomas and other M+/MO tumors. The inventive method of prediction and targeted therapy is applicable to any tumor that exists in both M+ and MO forms, such as the neurotumors glioma, neuroblastoma and ependymoma, as well as lung and breast cancers.